OPIOIDS AND HAEMODIALYSIS

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THE PRINCE OF WALES HOSPITAL

BACKGROUND

Estimated prevalence of chronic pain is >5-6 fold higher in haemodialysis patients compared to the general population

Reported prevalence of acute pain (30-80%) and chronic pain (20-90%) in haemodialysis patients (systematic reviews)

Up to 75% of pain reported as 'severe'

>60% haemodialysis patients receive annual opioid prescriptions (USRDS)

Kimmel, *JASN* 2017
Davison, *Semin Dial* 2014
Brkovic, *Patient Prefer Adherence* 2016
Murtagh, *Adv Chronic Kidney Disease* 2007

ESKD: DIVERSE PAIN AETIOLOGY

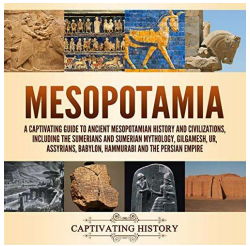
COMORBIDITIES	Diabetes Peripheral vascular disease Ischaemic heart disease Carpal tunnel syndrome Osteoarthritis
CHRONIC KIDNEY DISEASE	Renal osteodystrophy Uraemic neuropathy Calcific arteriopathy (calciphylaxis) Restless leg syndrome Gout
PRIMARY KIDNEY DISEASE	APCKD complications (acute/chronic) Post-transplant complications Nephrolithiasis Vasculitis
DIALYSIS	Headache Arthropathy Muscle cramps Steal syndrome AVF cannulation pain Ulnar nerve neuropathy Carpal tunnel syndrome Restless leg syndrome PD-associated (abdominal distension/lower back pain)

Lu, *Am J Kidney Dis* 2021

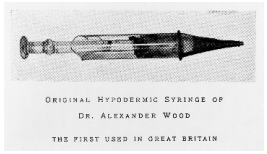
OPIOIDS: HISTORICAL PERSPECTIVE

OPIUM POPPY

3400 BC



MEDICINAL 'ANALGESIA'



'POTENT' PARENTERAL EFFECTS

1800s

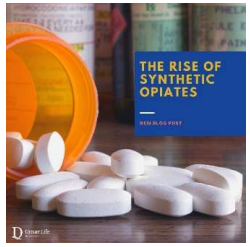
'EUPHORIA'

AMERICAN CIVIL WAR

HOUSEHOLD USE

1900s

NEWER OPIOID FORMULATION

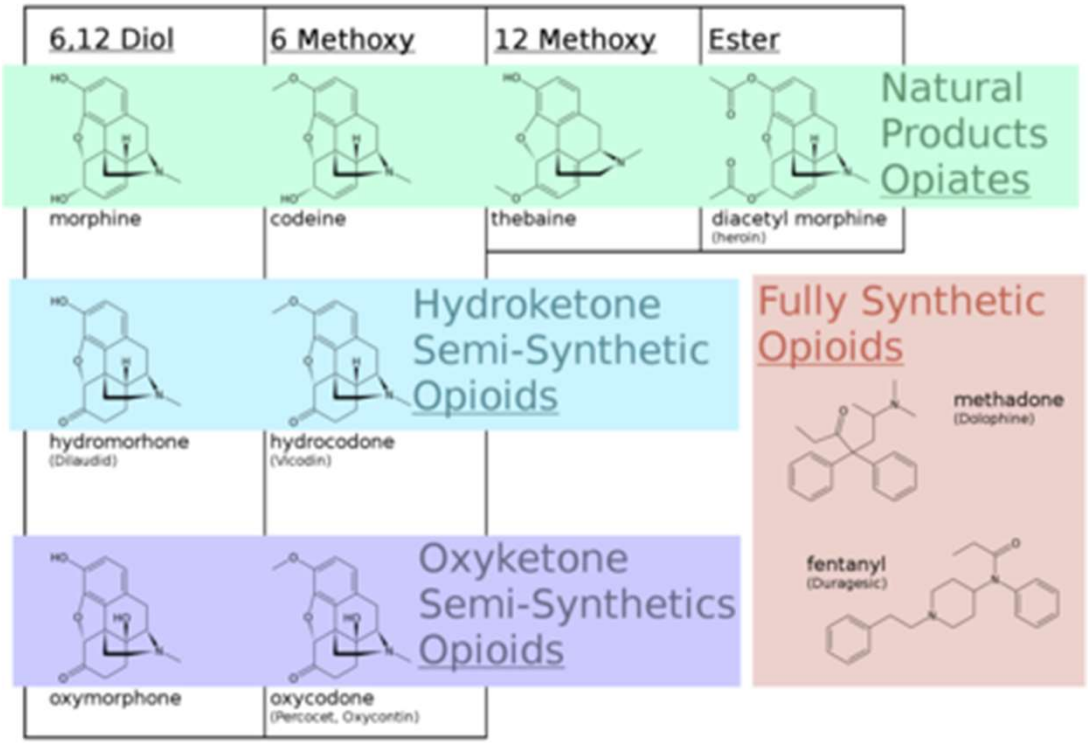


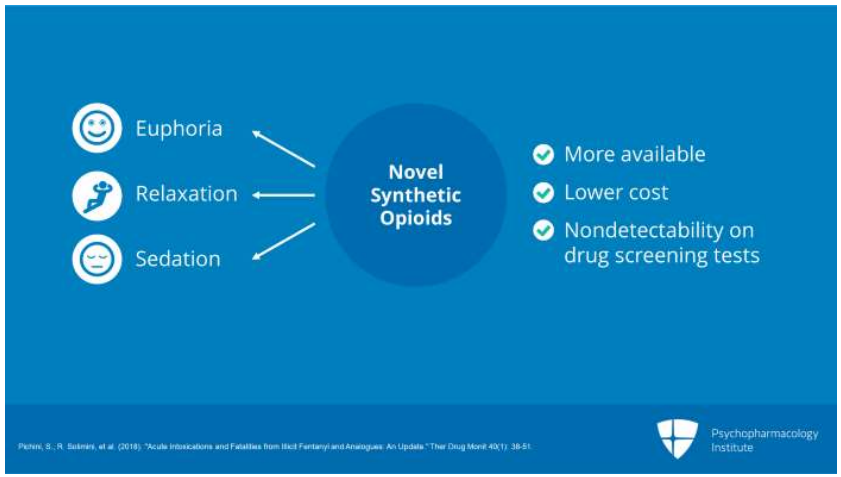
NON-CLINICAL OPIOIDS CRIMINALISED

2000s

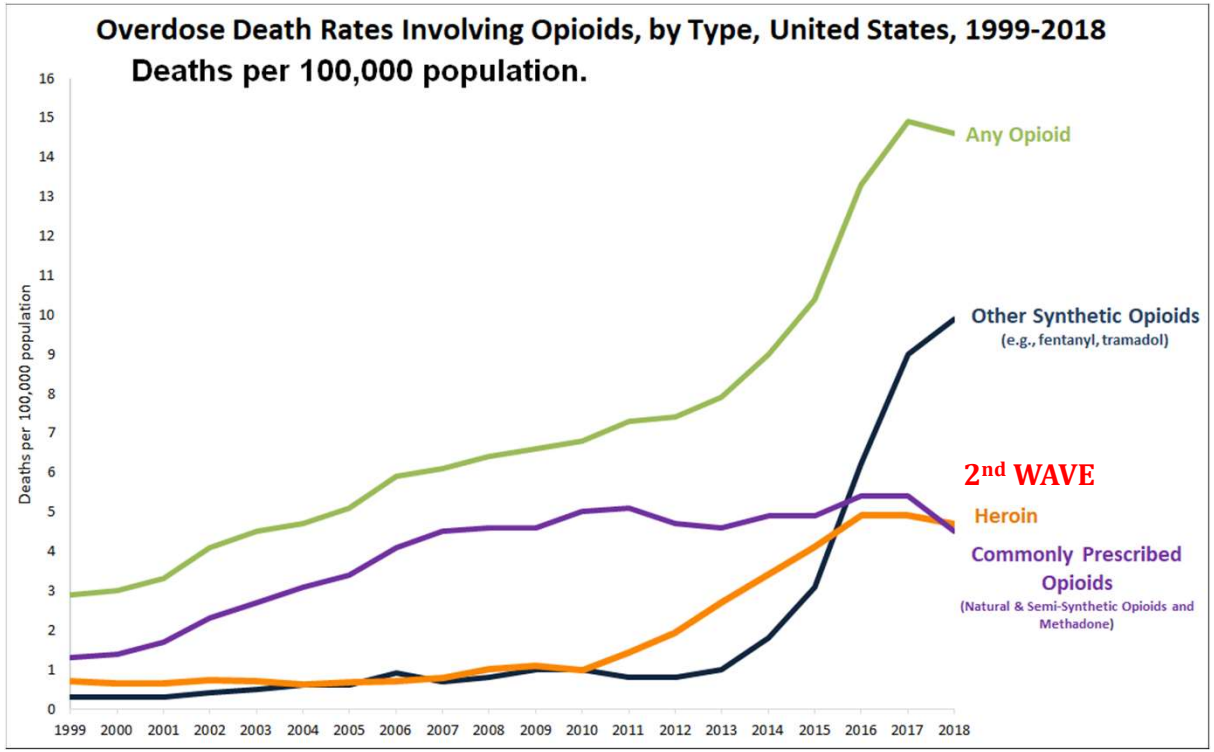
OPIOID EPIDEMIC

OPIOID DRUG DEVELOPMENT



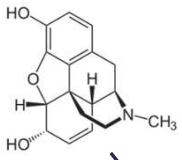


OPIOID EPIDEMIC: WAVES OVER TIME



OPIOID PHARMACOKINETICS & CKD

OPIOIDS



CYP2D6
CYP3A4

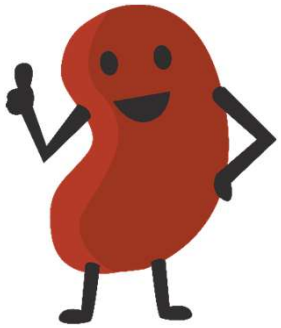
HEPATIC METABOLISM
(1ST PASS)

GLUCURONIDATION

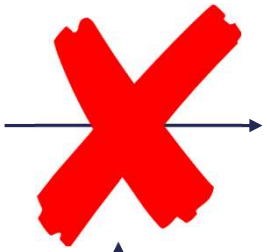
ACTIVE METABOLITES

INACTIVE METABOLITES

RENAL ELIMINATION

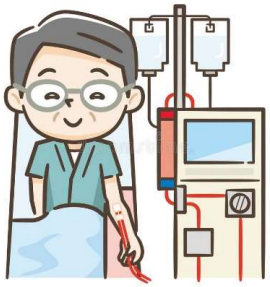


ANURIA



URINE EXCRETION

DIALYTIC CLEARANCE

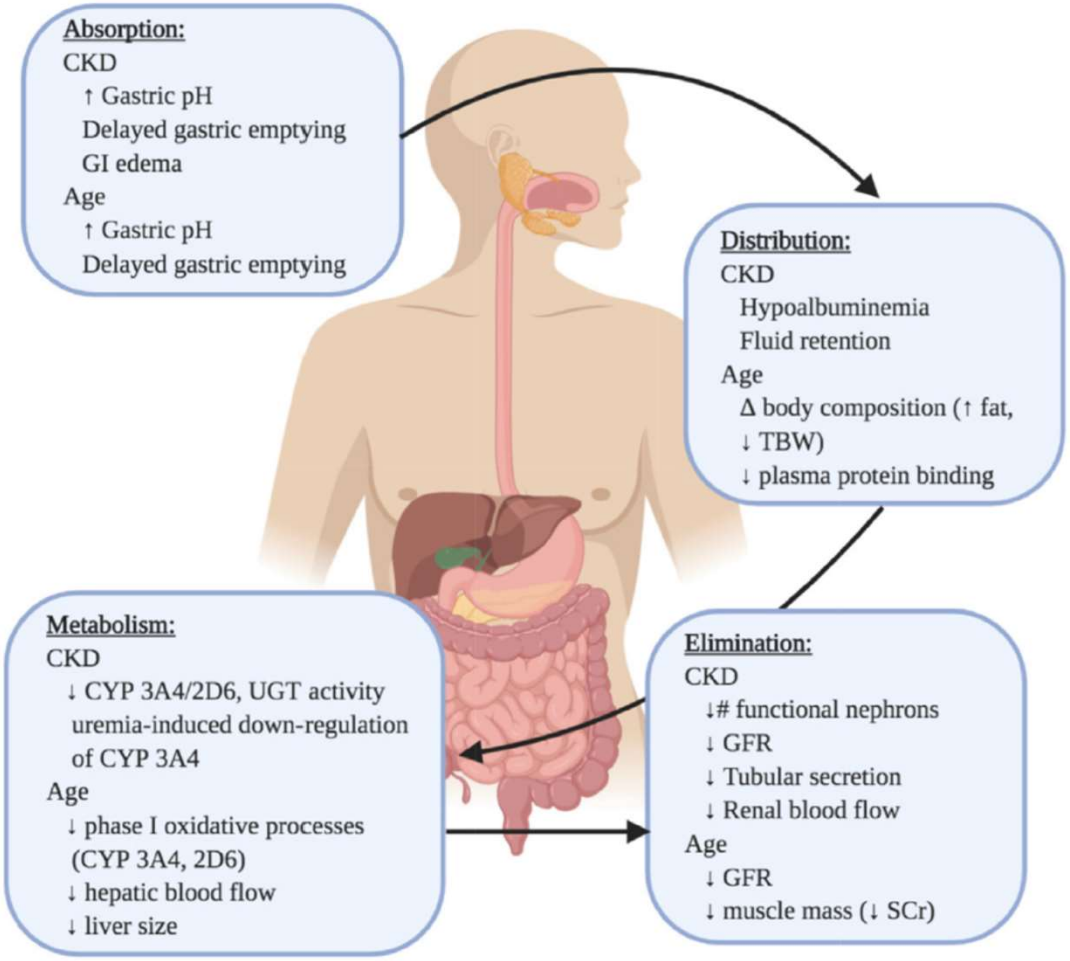


PROTEIN BINDING
WATER SOLUBILITY
MOLECULAR WEIGHT
DISTRIBUTION VOLUME

UNPREDICTABLE LEVELS OF OPIOID ACTIVE/INACTIVE METABOLITES

Kalim, *Semin Dial* 2021
Hawley, *Semin Dial* 2021

CKD EFFECTS: OPIOID PHARMACOKINETICS



Lu, *Am J Kidney Dis* 2021

OPIOID PHARMACOKINETICS: DIALYSIS EFFECTS

Major concerns regarding opioid/metabolite accumulation with prolonged adverse effects in CKD patients (narrow efficacy:harm window)

Some active metabolites more potent than initial parent compound!!

Data on haemodialysis effects upon opioid pharmacokinetics is (extremely) limited

?haemodialysis patients require increased dosing interval frequency

OPIOID PHARMACOKINETICS: DIALYSIS EFFECTS

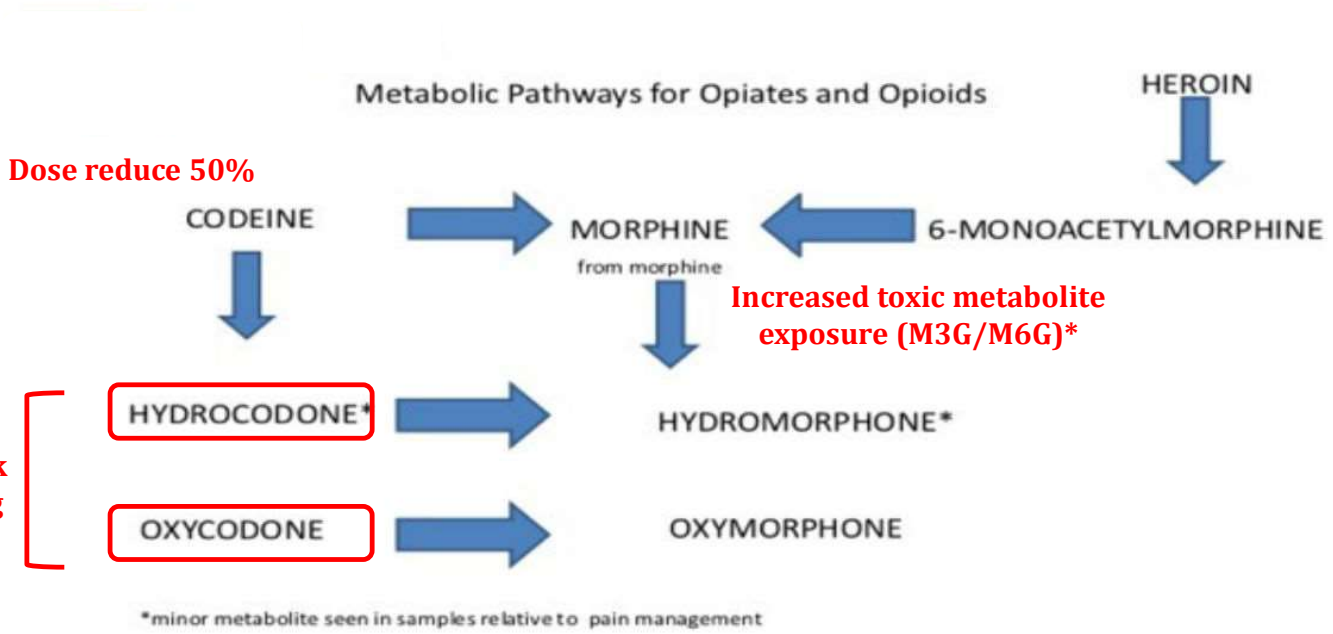
Opioids with significant dialytic clearance may cause withdrawal symptoms during/after dialysis session (?should there be dose supplementation)

Haemodialysis patients require increased dosing interval (?misconception)

- **Majority 1st pass hepatic metabolism**
- **Inactive metabolites produced with little analgesic effect but other potential toxicity**
- **Increased pain due to loss of opioid effects**
- **Potentially longer exposure duration to other toxic metabolites**

Opioid selection should be based upon metabolite profile

OPIOID METABOLIC PATHWAYS



M3G; morphine-3-glucuronide
M6G; morphine-6-glucuronide

Kalim, *Semin Dial* 2021

OPIOID TYPE OVERVIEW

Opioid	Degree of Renal Elimination	Active Metabolite	Dialyzable	Use in CrCl <30 mL/min or in Hemodialysis
Buprenorphine	Moderate (30%)	Yes	No	Caution
Codeine	Extensive (90%)	Yes	Yes	Avoid
Fentanyl	Minimal (7%-10%)	No	No	Caution
Hydrocodone	Moderate (25%)	Yes	Yes	Caution
Hydromorphone	Extensive	Yes	Yes	Caution
Methadone	Moderate	No	No	Caution
Morphine	Extensive	Yes	Yes*	Avoid
Oxycodone	Extensive	Yes	Yes	Caution
Tramadol*	Moderate (30%)	Yes	Yes	Avoid

***Excreted primarily in urine (30% unchanged & 60% active metabolites)**
High risk accumulation/neurotoxicity

OPIOID: HAEMODIALYSIS PREFERRED

	BIOLOGY	DIALYSABILITY	PROPERTIES	ADVERSE EFFECTS
Fentanyl	High molecular weight High protein binding High distribution volume Low water solubility	Nil significant	Inactive primary metabolite (norfentanyl) Initiate 50% usual dose	Respiratory depression
Hydromorphone	Low molecular weight Low protein binding Low distribution volume High water solubility	Extensive (40% reduction)	Interdialytic principal metabolite accumulation* Initiate 25% usual dose	Ataxia Myoclonus Convulsions Cognitive impairment
Buprenorphine	High molecular weight High protein binding High water solubility	Nil significant	Limited renal excretion (fecal route)	Insomnia Headache Abdominal pain
Methadone	High molecular weight High protein binding High distribution volume Low water solubility	Nil significant	Analgesic ½ life shorter than elimination ½ life (?potential toxicity even after analgesia effects worn off)	QTc prolongation

*hydromorphone-3-glucuronide

Hawley, *Semin Dial* 2021

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*hydromorphone-3-glucuronide

Hawley, *Semin Dial* 2021

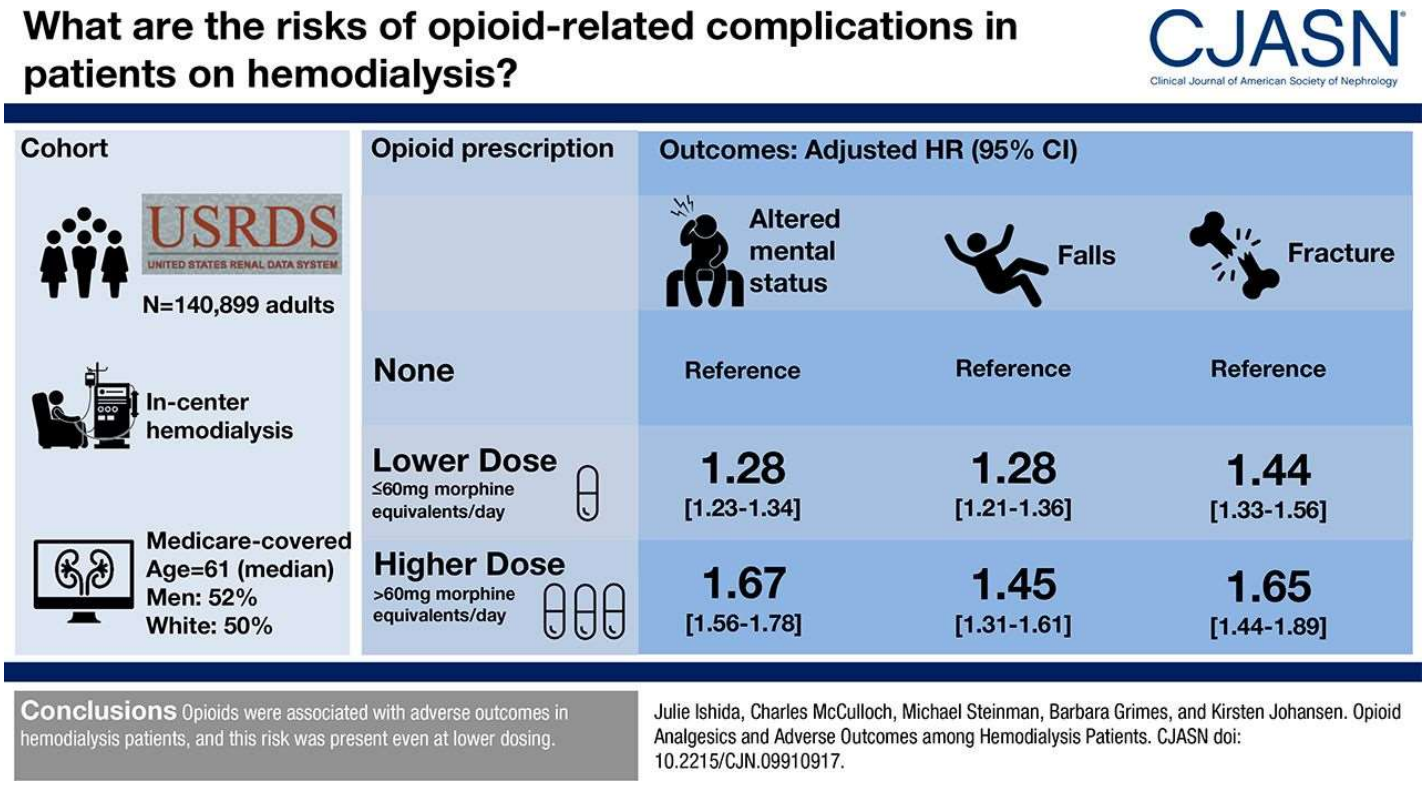
OPIOIDS: ADVERSE OUTCOMES IN ESKD

Characteristics	Outcome: Death			Outcome: Discontinued Dialysis			Outcome: Hospitalization		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Opioid prescription[a]									
None	1.00			1.00			1.00		
Short term	1.05	1.02 to 1.07	<0.001	1.13	1.05 to 1.22	0.002	1.13	1.11 to 1.14	<0.001
Chronic, <20 MME/d	1.16	1.11 to 1.21	<0.001	1.32	1.15 to 1.53	<0.001	1.26	1.22 to 1.29	<0.001
Chronic, 20–50 MME/d	1.26	1.22 to 1.30	<0.001	1.36	1.22 to 1.51	<0.001	1.29	1.27 to 1.32	<0.001
Chronic, 50+ MME/d	1.39	1.34 to 1.44	<0.001	1.47	1.30 to 1.66	<0.001	1.38	1.35 to 1.41	<0.001

Do opiates cause increased risk of death in haemodialysis (mechanism unclear)?

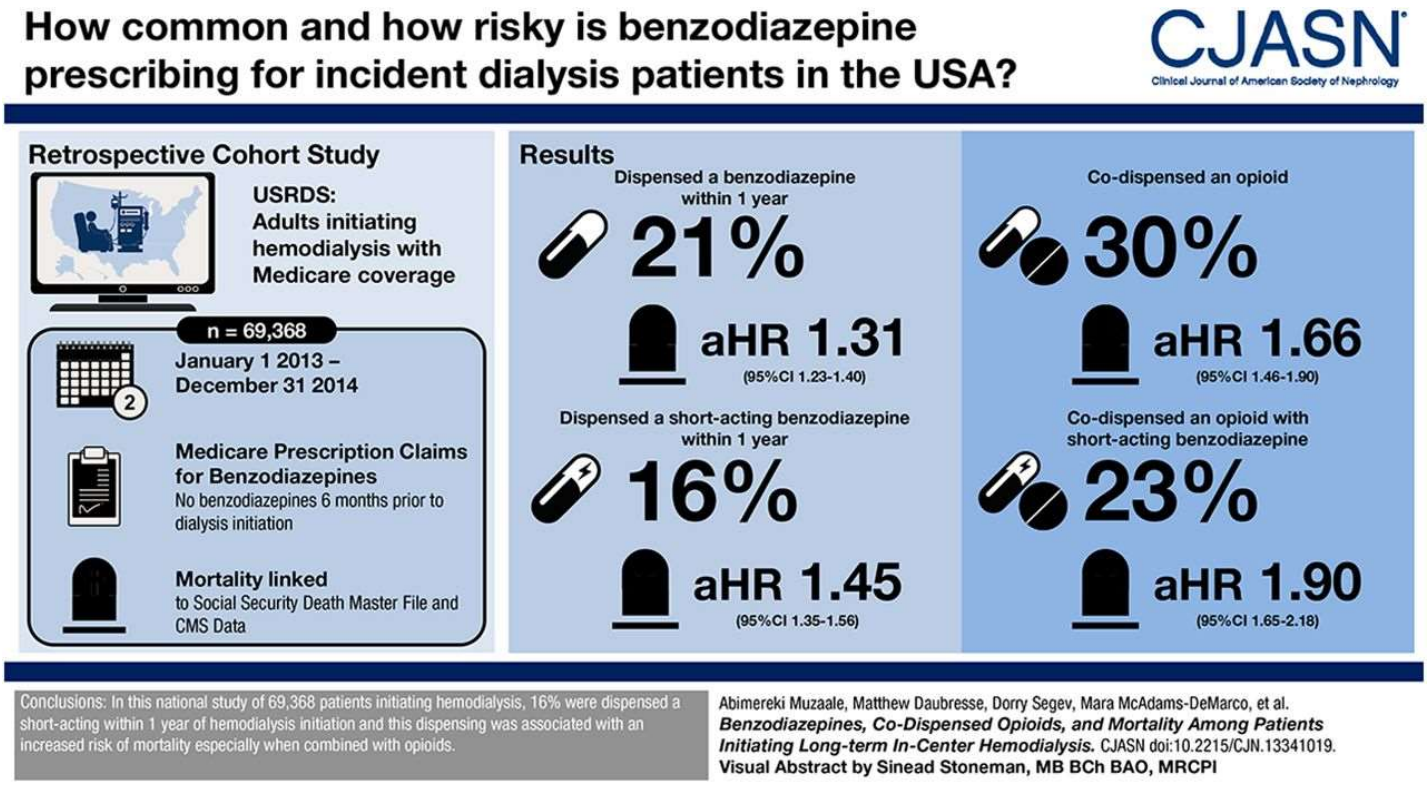
Kimmel, *JASN* 2017

OPIOIDS: ADVERSE OUTCOMES IN ESKD



Ishida, *CJASN* 2018

OPIOID & BENZODIAZEPINES: CUMULATIVE TOXICITY



Muzaale, *CJASN* 2020

OPIOIDS & GABAPENTINOIDS

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Concomitant Use of Gabapentinoids with Opioids Is Associated with Increased Mortality and Morbidity among Dialysis Patients

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Waddy, *Am J Nephrol* 2020

SUMMARY

Opioid use is highly prevalent in the haemodialysis population

All opioids should be used with caution (preferably short course only) in CKD patients with avoidance of those with predominant renal excretion & risk of toxic metabolite excretion

Consider concomitant use of non-pharmacological analgesic therapies

Potential mortality/morbidity risks & poor understanding of opioid pharmacokinetics underscores critical need for ongoing research to inform best approach for pain management in ESKD patients